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PREPARATION OF CHAULMOOGRA OIL DERIVATIVES FOR THE TREATMENT OF LEPROSY.

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The following description is written to meet the request for a brief statement of the routine methods used at the University of Hawaii for making certain derivatives of chaulmoogra oil for therapeutic use.

The chaulmoogra oil used is obtained through the dealers and varies greatly in quality. Some lots are clear and liquid at our laboratory temperature (usually between 70° and 80° F.); others are dark, muddy looking oils with large quantities of precipitated material. The genuine chaulmoogra oil is expressed from the seeds of *Taraktogenos kurzii*. A number of closely related species of Hydnocarpus yield oils of similar composition, and some of the commercial oils are quite likely to be Hydnocarpus oils or mixtures of Hydnocarpus and Taraktogenos oils. There is probably little or no difference in the values of these oils for purposes of making preparations to be used in leprosy. The distinguishing characteristic of all of these oils is their power of rotating the plane of polarized light. The valuable oils show specific rotations around +50°. The differences in appearance noted above seem to have no correlation with differences in rotation, and quite satisfactory products can be made from oils of poor appearance.

The first step is to break up the glycerides into glycerol and the sodium soaps of the fatty acids by saponifying the oil with sodium hydroxide under pressure. Two hundred and forty grams of sodium hydroxide are dissolved in 1 liter of hot water, and this is thoroughly mixed with 1,500 grams of chaulmoogra oil in a 5-liter, round-bottom flask, and heated in an autoclave under 15 pounds of steam pressure for one hour. Loss by frothing is prevented by inserting a loosely fitting wooden plug or stopper in the neck of the flask, through which runs a piece of 16 mm. (inside diameter) glass tubing, which extends about 35 cm. above the flask, where two right-angle bends lead it into an 800 c. c. beaker, placed on a shelf in the autoclave.

A piece of cheesecloth tied over the top of the beaker, through which the bent tube projects, effectively prevents loss from spattering.

When the reaction is complete, the mixture is poured into 3 or 4 liters of hot water in a large precipitating jar and stirred until dissolved. The soap solution is now acidified with commercial hydrochloric acid, and the liberated fatty acids rise to the top of the water in the form of a thick oily layer. By means of a siphon, the lower aqueous layer containing sodium chloride and glycerol is drawn off and discarded. The remaining oil is washed with successive portions of hot water and finally transferred to a hot-water funnel, where, in the course of a few hours' heating, all the water settles out from the liquefied fatty acids and is drawn off. The acids are strained through linen before being allowed to solidify. The usual yield of mixed fatty acids at this point is between 1,350 and 1,400 grams.

These crude mixed fatty acids are treated in different ways to prepare the products which are described under the following headings: (*a*) Mixed ethyl esters, (*b*) Capsules, (*c*) Ethyl hydnocarpate, (*d*) Ethyl chaulmoograte, (*e*) Ethyl dihydrochaulmoograte.

Mixed ethyl esters (for intramuscular injection).—Mixed ethyl esters are prepared by esterifying the crude mixed fatty acids with ethyl alcohol. Eight hundred cubic centimeters of 92–94 per cent ethyl alcohol are added to 1,000 grams of acids in a 2-liter flat-bottom flask, heated to 50°–60° C., under a reflux condenser, and dry hydrochloric acid gas is led into the flask. This treatment is continued for about 20 minutes after a separation into two layers occurs. The hydrochloric acid gas is conveniently prepared by allowing concentrated sulphuric acid to drop into concentrated hydrochloric acid and drying the hydrogen chloride gas evolved by passing it through sulphuric acid.

When esterification is complete, the contents of the flask are poured into 2 or 3 liters of warm water and washed to remove excess hydrochloric acid and alcohol. The ethyl esters come to the top on standing, and the lower aqueous layer is siphoned off and discarded. The washing is continued with several successive portions of water. Any water held emulsified in the esters settles out upon being held for a time in a hot water funnel. These crude ethyl esters are reddish-brown in color. They can be used in this condition; but in order to get them as pure as possible they are distilled under high vacuum.

About 1,200 c. c. of the crude dry esters are put in a 2-liter distilling flask. A roll of wire gauze is inserted in the lower part of the neck of the flask and the neck is filled with glass beads or short lengths of glass tubing to form a fractionating column about

12 cm. in length. The flask is connected to the vacuum pump through a specially designed piece of apparatus with stopcocks so arranged that the receiver may be changed without interfering in any way with the distillation. (See Fig. 1.)

Capsules (for administration by way of the mouth).—Capsules are prepared by melting the mixed fatty acids and running the liquid into gelatine capsules of varying sizes containing $\frac{1}{6}$, $\frac{1}{3}$, $\frac{1}{2}$, and $\frac{2}{3}$ gram of the fatty acids. When cool, the contents of the capsules become solid.

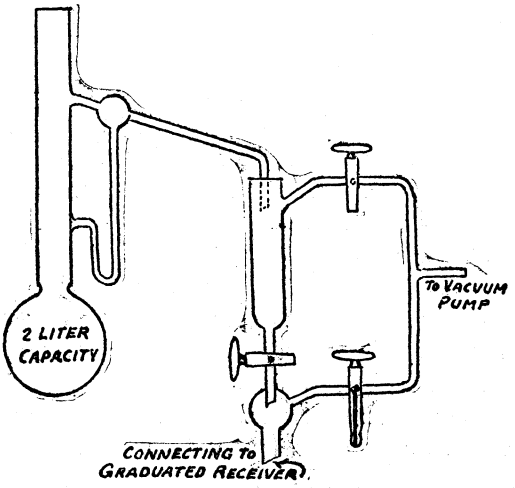

FIG. 1.

Distillation of the mixed fatty acids.—From the mixture of fatty acids, pure chaulmoogric acid and pure hydnocarpic acid have been prepared by fractional distillation under high vacuum followed by a fractional crystallization, using the same apparatus as that described for distilling the ethyl esters.

The vacuum is applied before the temperature of the liquid in the flask rises above 100° C; otherwise serious frothing may result. It is best to have both stopcocks open to the vacuum, also the stopcock leading into the graduated receiver. There is usually a tendency for a little of the fatty acid vapor to solidify in the stopcocks, interfering with the vacuum. This difficulty may be obviated by playing a jet of steam against the stopcock. As the stopcocks must remain air-tight, even while hot, it is best to use a mixture of vaseline and talcum powder as a lubricant in them. Some of the patent stopcock lubricants also give good results.

The first 350 c. c. which distill over are worked for hydnocarpic acid. The next 200, composing the mixture fraction, are set aside to be redistilled as part of the next lot of mixed fatty acids. The remainder of the distillate is worked for chaulmoogric acid.

Ethyl hydnocarpate.—The hydnocarpic acid fraction noted above is recrystallized first from 80 per cent alcohol, using 20 c. c. of alcohol per 5 grams of acid, and recrystallization is continued from this solvent until the melting point of the solute is above 35° C.; then it is recrystallized from petroleum ether, using 30 c. c. of solvent per 5 grams of solute until its melting point is 60° C. The melting point of the

product from each crystallization moves upward very slowly in the case of this acid, from 12 to 16 recrystallizations being required to purify the acid completely and bring its melting point up to 60° C.

The hydnocarpic acid is esterified with ethyl alcohol in the same way that the mixed acids are, and the ethyl hydnocarpate is washed, dried, and distilled under high vacuum. The ethyl hydnocarpate is almost water white.

Ethyl chaulmoograte.—The chaulmoogric acid fraction is recrystallized from 80 per cent alcohol, using 20 c. c. of the alcohol to 5 grams of the acid, and recrystallization is continued until the product melts at 68° C. In general, four or five crystallizations are sufficient.

The pure chaulmoogric acid is treated with ethyl alcohol and esterified in the same manner as the mixed acids. The ethyl chaulmoograte is washed, dried, and distilled under high vacuum. It is almost water white in color.

Dihydrochaulmoogric acid and ethyl dihydrochaulmoograte.—Dihydrochaulmoogric acid is prepared from pure chaulmoogric acid by catalytic reduction. Two hydrogen atoms enter the double bond of chaulmoogric acid forming a saturated inactive acid.

One hundred grams of chaulmoogric acid are dissolved in 150 c. c. of 95 per cent ethyl alcohol. The flask containing the solution is kept at a temperature of 55–60° C. in a water bath, and hydrogen under 2–3 pounds pressure is bubbled through the solution. The catalyst, prepared as follows, is added to this solution: Five c. c. of a solution of platinum chloride ($Pt. Cl_4$), containing 0.01 gram of platinum per c. c., and 5 c. c. of a solution of palladium chloride ($Pd. Cl_2$), containing 0.01 gram of palladium per c. c., and 3 c. c. of a solution containing 0.01 gram of gum arabic per c. c. are mixed, and about 2 grams of hydroxylamine-hydrochloride added; then, with constant stirring, small amounts of sodium bicarbonate are added until the color due to the chloride disappears and a transluscent black begins to appear. It is then immediately added to the chaulmoogric acid solution.

The time necessary for complete reduction of the chaulmoogric acid varies from 24 hours to several days, and it is frequently necessary to add fresh portions of the catalyst from time to time. The reduction can be measured by taking samples at intervals and determining the iodine value. The iodine value of dihydrochaulmoogric acid is zero.

The pure dihydrochaulmoogric acid is obtained by recrystallizing from glacial acetic acid.

Ethyl dihydrochaulmoograte is obtained by treating the acid with ethyl alcohol. As this acid is much harder to esterify than any of the others, it is necessary to use absolute ethyl alcohol in excess and to pass in the hydrogen chloride until the solution is saturated, in

order to get complete esterification. The ethyl dihydrochaulmoograte is washed, dried, and distilled in the same manner as the mixed esters.

HYGIENIC LABORATORY NOTE.—For reference to the earlier work on the chemistry of chaulmoogra oil and its derivatives the following references may be consulted:

The Constitution of Chaulmoogric Acid, Part I. By Power and Gornall. Published in the Transactions of the Chemical Society, 1904.

The Constituents of the Seeds of Gynocardia Odorata, R. Br. By Power and Barrowcliff. Published in the Transactions of the Chemical Society, 1905.

The Constitution of Chaulmoogric and Hydnocarpic Acids. By Barrowcliff and Power. Published in the Transactions of the Chemical Society, 1907.

The foregoing were all published as reprints from the Wellcome Chemical Research Laboratories, Frederick B. Power, Director. These papers were referred to in an earlier paper by Professor Dean and Doctor Wrenshall, entitled "Fractionation of Chaulmoogra Oil," Reprint No. 646, from the Public Health Reports, April 1, 1921.

THE NOTIFIABLE DISEASES.

PREVALENCE DURING 1921 IN CITIES OF OVER 100,000.[1]

ANTHRAX, CEREBROSPINAL MENINGITIS, DIPHTHERIA, INFLUENZA, MALARIA, MEASLES PELLAGRA, PNEUMONIA (ALL FORMS), POLIOMYELITIS (INFANTILE PARALYSIS), RABIES IN ANIMALS, RABIES IN MAN, SCARLET FEVER, SMALLPOX, TUBERCULOSIS (ALL FORMS AND PULMONARY), TYPHOID FEVER, AND TYPHUS FEVER—CASES AND DEATHS REPORTED, 1921; INDICATED CASE AND DEATH RATES PER 1,000 POPULATION; FATALITY RATES PER 100 CASES; AND MEDIAN NUMBER OF CASES REPORTED DURING PRECEDING YEARS.

The following tables were compiled from data furnished by the city health officers. They include all cities in the United States of 100,000 population or over.

The populations given, and which were used in computing the rates, were estimated as of July 1, 1921, except where otherwise stated. For cities which are included in the Weekly Health Index, issued by the Bureau of the Census, the estimated populations as given in that publication were used. Estimates based on the censuses of April 15, 1910, and of January 1, 1920, were made for other cities.

The figures given are for the calendar year 1921, except for Portland, Oreg., where the year began December 1, 1920, and ended November 30, 1921.

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[1] It will be noted that some of the cities are apparently much more successful in obtaining reports of the notifiable diseases than are others. This may be due to the greater activity of their health departments or to a greater interest in the public welfare on the part of their practicing physicians. That the health departments of certain cities are securing fairly complete information of the prevalence of preventable diseases is indicated in a number of instances by the large numbers of cases reported as compared with the numbers of deaths registered from the same causes.